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PATENT SPECIFICATION (11) 1269291

1269291

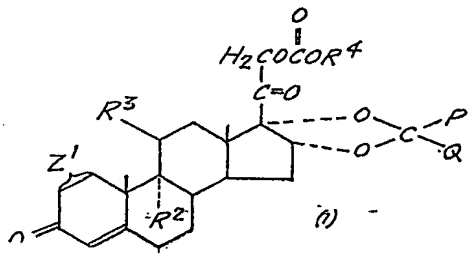
NO DRAWINGS

(21) Application No. 16444/70 (22) Filed 7 April 1970
(31) Convention Application No. 817564 (32) Filed 18 April 1969 in
(33) United States of America (US)
(45) Complete Specification published 6 April 1972
(51) International Classification C 07 c 173/00
(52) Index at acceptance
C2U 2 3 4A2 4B2 4C4 4C5 4D 4X

(54) IMPROVEMENTS IN OR RELATING TO CORTICOID CARBONATES

(71) We, SYNTEX CORPORATION, a Panamanian Corporation of Apartado Postal 7386, Panama, Panama, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel cyclopentanophenanthrene derivatives. More particularly, this invention is directed to 21-corticoid carbonates which can be represented by the following general formula:



(I)

ERRATA

SPECIFICATION No. 1,269,291

Page 4, line 24, *for* cyclopropyl *read* cyclopropylethyl

Page 5, line 3, *for* p-chlororopiophenone *read* p-chloropropiophenone

Page 5, line 24, *for* determind *read* determined

THE PATENT OFFICE
14th June 1972

positions comprising compounds of formula I in suitable [illegible]

The term "lower alkyl" and derivations thereof appearing in the above definitions and elsewhere in the instant specification denote alkyl groups containing 1 to 6 carbon atoms, inclusive, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, amyl, hexyl, and the like. The term "cycloalkyl" denotes cycloalkyl groups having from 3 to 10 carbons such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, 3-(cyclohexyl)-

[*Price 25p*]

SEE ERRATA SLIP ATTACHED

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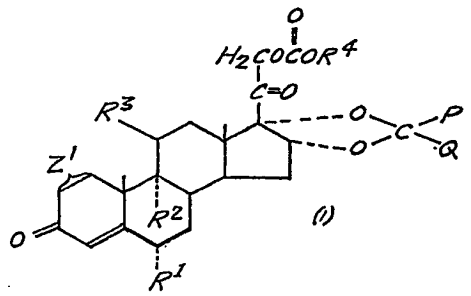


(I)

wherein,

R^1 is fluoro or chloro;

R^2 is hydrogen, fluoro or chloro;

R^3 is hydroxy or when R^2 is chloro, R^3 can be chloro;

R^4 is lower alkyl, cycloalkyl, or aralkyl;

P and Q are hydrogen, lower alkyl, halogenated lower alkyl monocyclic cycloalkyl, monocyclic aryl, monocyclic aryl lower alkyl, monocyclic heterocyclic, or monocyclic heterocyclic lower alkyl, or together with the carbon atoms to which they are joined P and Q are cycloalkyl or monocyclic heterocyclic; and

Z^1 is a single or double bond.

The above novel compounds of this invention have anti-inflammatory, glycogenic, thymolytic, anti-estrogenic and anti-androgenic activity and can be used in the same manner for the same purposes as 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide (fluocinolone acetonide). They are particularly useful for topical treatment of skin inflammation and similar skin disorders, and for this purpose can be used together with the conventional excipients in the conventional bases used for topical preparation. The invention includes therapeutic compositions comprising compounds of formula I in suitable pharmaceutical excipients.

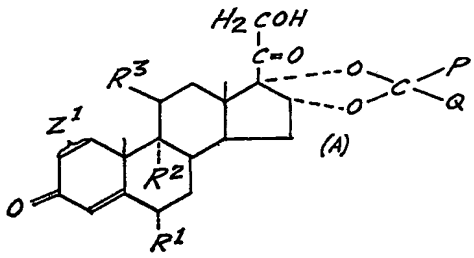
The term "lower alkyl" and derivations thereof appearing in the above definitions and elsewhere in the instant specification denote alkyl groups containing 1 to 6 carbon atoms, inclusive, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, amyl, hexyl, and the like. The term "cycloalkyl" denotes cycloalkyl groups having from 3 to 10 carbons such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, 3-(cyclohexyl)-

[Price 25p]

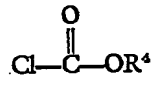
SEE ERRATA SLIP ATTACHED

propyl, and the like. The term "aralkyl" and derivations thereof appearing in the above definitions and elsewhere in the instant specification denote phenylalkyl and substituted phenylalkyl groups containing from 7 to 10 carbon atoms, inclusive, such as benzyl, *o*-, *m*- and *p*-methylbenzyl, phenylethyl and 3-(phenyl)propyl.

The compounds of Formula I are prepared according to this invention by reacting a steroid of the general formula



wherein R^1, R^2, R^3, P, Q and Z^1 are as previously defined with a chloroformate having the general formula:



(B)

wherein R^4 is as previously defined. The steroid of Formula A can be reacted in a pyridine solution with the chlorocarbonate of Formula B in excess of one mole of the steroid. The reaction can be conducted in the presence of a cosolvent such as chloroform, dichloromethane, monoglyme, or tetrahydrofuran since the neat pyridine solution may cause some decomposition of certain of the reactants. The reaction is conducted at a temperature of from −70° to 20°C, for from 5 to 48 hours, preferably for 18 hours at 0°C, and purified by conventional procedures. For example, the reaction mixture containing the product carbonate can be diluted with water, filtered, and the solid product dried and purified by crystallization or chromatography on silica gel to yield the 21-corticoid carbonates of Formula I.

The chloroformates of Formula B together with representative procedures for reacting them with steroids are disclosed in U.S. Patents 3,056,727, 3,314,856, 3,329,570, 3,409,641 and Belgium Patent 706,333. In general, the chloroformates are formed by reacting a corresponding alcohol with an excess of phosgene in a suitable inert organic solvent to obtain the chlorocarbonate. For example, phosgene can be allowed to bubble for a period of 1.5 hours into 120 cc. of anhydrous ethanol cooled to 0°C. Then 30 g. of cyclohexylmethanol is introduced. The reaction mixture is then agitated at 0°C for a period of 24 hours, the phosgene is removed by bubbling nitrogen therethrough, and the mixture is concentrated to dryness under vacuum to yield the cyclohexylmethyl chloroformate.

Other suitable chloroformates include methyl chloroformate, ethyl chloroformate, n-propyl chloroformate, cyclohexyl chloroformate and benzyl chloroformate.

The compounds of Formula A are described together with methods for their preparation in U.S. Patent 3,053,838. Among the suitable starting steroids useful in the process of this invention can be mentioned the 16α,17α-acetal derivatives of

6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione,
6α-chloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione,
6α,9α-dichloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione,
6α-chloro-9α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione,
6α,9α,11β-trichloro-16α,17α,21-trihydroxypregn-4-ene-3,20-dione,
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxypregn-4-ene-3,20-dione,
6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione,
6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione,

6α,9α-dichloro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione,
6α-chloro-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione,
6α,9α,11β-trichloro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione, and
9α,11β-dichloro-6α-fluoro 16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione,

with lower alkanals such as paraldehyde, propanal, and hexanal; halogenated lower alkanals such as chloral hydrate trifluoroacetaldehyde hemiacetal and hepta fluorobutanal ethyl hemiacetal; di(lower alkyl)ketones, such as acetone, diethylketone, dibutylketone, methylethylketone, and methylisobutylketone; halogenated di(lower alkyl)ketones, such as 1,1,1-trifluoroacetone; cycloalkanones, such as cyclopentanone, cyclohexanone, suberone, cyclobutanone, and cyclodecanone; mono- and dicycloalkyl ketones, such as cyclohexylmethyl ketone and dicyclopropyl ketone; monocyclic aromatic aldehydes, such as benzaldehyde, halobenzaldehydes (e.g. *p*-chlorobenzaldehyde and *p*-fluorobenzaldehyde), lower alkoxy benzaldehydes (e.g. *o*-anisaldehyde), di(lower alkoxy)benzaldehydes (e.g. veratraldehyde), hydroxybenzaldehydes (e.g. salicylaldehyde), dihydroxybenzaldehydes (e.g. resorcylaldehyde), lower alkyl benzaldehydes (e.g. *m*-tolualdehyde and *p*-ethylbenzaldehyde), di(lower alkyl)benzaldehydes (e.g. *o,p*-dimethylbenzaldehyde), nitrobenzaldehydes, acylamidobenzaldehydes (e.g. N-acetylanthranildaldehyde), and cyanobenzaldehydes; monocyclic aromatic lower alkanals, such as phenylacetaldehyde, α-phenylpropionaldehyde, β-phenylpropionaldehyde, γ-phenylbutyraldehyde, and aromatically-substituted halo, lower alkoxy, hydroxy, lower alkyl, nitro, acylamido and cyano derivatives thereof; monocyclic heterocyclic aldehydes, such as picolinaldehydes, furfural, thiophene carbonals and halo, lower alkoxy, hydroxy, lower alkyl, nitro, and cyano derivatives thereof; monocyclic heterocyclic lower alkanals; monocyclic aromatic lower alkyl ketones, such as acetophenone, propiophenone, butyrophenone, valerophenone, iso-caprophenone, halophenyl lower alkyl ketones (e.g. *p*-chloroacetophenone and *p*-chloropropiophenone), (lower alkoxy)-phenyl lower alkyl ketones (e.g. *p*-anisyl methyl ketone), di(lower alkoxy)phenyl lower alkyl ketones, hydroxyphenyl lower alkyl ketones, dihydroxphenyl lower alkyl ketones (e.g. resacetophenone), (lower alkyl)phenyl lower alkyl ketones (e.g. methyl *p*-tolyl ketone, di(lower alkyl)phenyl lower alkyl ketones (*o,p*-xylyl methyl ketone), nitrophenyl lower alkyl ketones (e.g. *p*-nitroacetophenone), acylamidophenyl lower alkyl ketones (e.g. acetylanilines), and cyanophenyl lower alkyl ketones; benzophenone, and mono or bis substituted halo, lower alkoxy, hydroxy, lower alkyl, nitro, acylamido and cyano derivatives thereof; monocyclic aromatic lower alkanones, such as 1-phenyl-3-butanone and 1-phenyl-4-pentanone, and aromatically substituted derivatives thereof; monocyclic heterocyclic ketones, such as 2-acetylfuran, 2-benzoylfuran, and 2-acetylthiophene; monocyclic heterocyclic lower alkanones; and monocyclic heterocyclic ketones, such as alloxan.

Example 1

Ethyl chloroformate (1 ml.) is added to a solution of 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide (500 mg.) in pyridine (15 ml.) at 0°C. The reaction mixture is maintained at 0°C for 18 hours, poured into water, filtered, washed with water, and crystallized from acetone-hexane to yield 6α,9α - difluoro - 11β,16α,17α,21 - tetrahydroxypregna - 1,4 - diene - 3,20 - dione 16α,17α-acetonide 21-ethyl-carbonate.

Example 2

Repeating the procedure of Example 1 with

6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-4-ene-3,20-dione 16α,17α-acetonide,

6α-chloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,

6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,

6α,9α-dichloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,

6α-chloro-9α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,

9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,

6α,9α,11β-trichloro-16α,17α,21-trihydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,

9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,
6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide,
6α-chloro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide,
6α-chloro-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide,
6α,9α,11β-trichloro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide, and
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide,
yields the corresponding 21-ethyl carbonates.

EXAMPLE 3

Repeating the procedures of Examples 1 and 2 but replacing ethyl chloroformate with methyl chloroformate, n-propyl chloroformate, n-pentyl chloroformate, cyclopropyl chloroformate, cyclopentyl chloroformate, cyclohexyl chloroformate, cyclopropylethyl chloroformate, cyclopentylmethyl chloroformate, cyclohexyl ethyl chloroformate, benzyl chloroformate, and *p*-methylbenzyl chloroformate yields the corresponding 21-methyl carbonate, 21 - (n - propyl)carbonate, 21 - (n - pentyl)carbonate, 21-cyclopropyl carbonate, 21-cyclopentyl carbonate, 21-cyclohexyl carbonate, 21-cyclopropyl carbonate, 21-cyclopentylmethyl carbonate, 21-cyclohexylethyl carbonate, 21-benzyl carbonate, and 21-(*p*-methylbenzyl)carbonate of
6α-fluoro-11β,16α,17α,21-tetrahydroxypreg-4-ene-3,20-dione 16α,17α-acetonide,
6α-chloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,
6α,9α-dichloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,
6α-chloro-9α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,
6α,9α,11β-trichloro-16α,17α,21-trihydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxypregn-4-ene-3,20-dione 16α,17α-acetonide,
6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide,
6α-chloro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide,
6α-chloro-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide,
6α,9α,11β-trichloro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide, and
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide.

EXAMPLE 4

Following the procedure of Example 1, 21-ethylcarbonates of 6α,9α - difluoro-11β,16α,17α,21 - tetrahydroxypregna - 1,4 - diene - 3,20 - dione 16α,17α - acetals, wherein the 16α,17α-acetal groups are acetals of propanal, hexanal, chloral hydrate, trifluoroacetaldehyde hemiacetal, hepta fluorobutanal ethyl hemiacetal, acetone, diethylketone, dibutylketone, methylethylketone, methylisobutylketone, 1,1,1-trifluoroacetone, cyclopentanone, cyclohexanone, suberone, cyclobutanone, cyclodecanone, cyclohexylmethylketone, dicyclopropylketone, benzaldehyde, *p*-chlorobenzaldehyde, *p*-fluorobenzaldehyde, *o*-anisaldehyde, veratraldehyde, salicylaldehyde, *m*-tolualdehyde, *p*-ethylbenzaldehyde, *o,p*-dimethylbenzaldehyde, phenylacetaldehyde, α-phenylpro-

pionaldehyde, β-phenylpropionaldehyde, picolinaldehyde, furfuraldehyde, acetophenone, propiophenone, butyrophenone, valerophenone, isocaprophenone, p-chloroacetophenone, p-chloropropiophenone, p-anisyl methyl ketone, methyl p-tolyl ketone, α,p-xylyl methyl ketone, benzophenone, 1-phenyl-3-butanone, 1-phenyl-4-pentanone, 2-acetylfuran, 2-benzoylfuran, 2-acetylthiophene, and alloxan are obtained from the corresponding 21-hydroxy compounds.

EXAMPLE 5

Improved anti-inflammatory activity of the compounds of this invention is demonstrated as follows. A "rat-ear" test was used to compare the anti-inflammatory activity of 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione-16α,17α-acetonide 21-ethylcarbonate (Compound A) with 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16α,17α-acetonide (Compound B) the latter compound being a commercial anti-inflammatory compound having the generic name fluocinolone acetonide.

The test is a modification of a method originally described by Tonelli, et al in Endocrinology 77, 625 (1965). A vehicle consisting of 20% pyridine, 5% distilled water, 74% diethyl ether and 1% croton oil is used. Intact male 21-day-old rats are anesthetized, and the test compound is inuncted onto the ear as follows: 0.05 ml. is inuncted onto the inside of the left ear and 0.05 ml. is inuncted onto the outside of the left ear. The vehicle containing the irritant is given simultaneously with the anti-inflammatory compound. Rats in a control group receive only the vehicle. Both ears are removed 6 hours after administration of the compound, and pieces of uniform size are punched out with a No. 4 cork borer. The pieces of ear are then weighed and the difference in weight increase between the two pieces of ear are determind.

The data obtained is summarized in Table 1 showing the activity in comparison with the activity of hydrocortisone.

Table 1

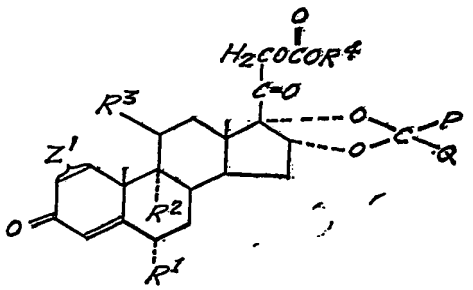
Compound	No. of rats	Dose range tested, μg.	Activity[a]
A	84	0.1 —2.7	390
B	235	0.05—2.7	150

[a] hydrocortisone has an activity value of one.

As can be readily seen from the data in Table 1, as measured by the rat-ear test, the 21-ethylcarbonate is 2.6 times as active as the corresponding 21-hydroxy compound.

WHAT WE CLAIM IS:—

1. A compound of the formula:



wherein

R^1 is fluoro or chloro;

R^2 is hydrogen, fluoro or chloro;

R^3 is hydroxy or when R^2 is chloro, R^3 can be chloro;

R^4 is lower alkyl, cycloalkyl or aralkyl;

P and Q are hydrogen, lower alkyl, halogenated lower alkyl, monocyclic cycloalkyl, monocyclic aryl, monocyclic aryl lower alkyl, monocyclic heterocyclic or monocyclic heterocyclic lower alkyl or together with the carbon atoms to which they are joined P and Q are cycloalkyl or monocyclic heterocyclic and

Z^1 is a single or double bond.

2. A compound of Claim 1 wherein R^4 is methyl, ethyl, n-propyl, cyclohexyl, or cyclohexylmethyl.

3. A compound of Claim 1 wherein R^4 is lower alkyl.

4. A compound of Claim 3 wherein P and Q, together with the carbon atom to which they are joined are cyclopentyl or cyclohexyl.

5. A compound of Claim 4 wherein R^2 is hydrogen.

6. A compound of Claim 4 wherein R^2 is fluoro.

7. A compound of Claim 3 wherein P and Q are methyl.

8. A compound of Claim 7 wherein R^2 is hydrogen.

9. As a compound of Claim 8, 6α - fluoro - 11β,21 - dihydroxy - 16α,17α - isopropylidenedioxypregn - 4 - ene - 3,20 - dione 21-ethyl-carbonate.

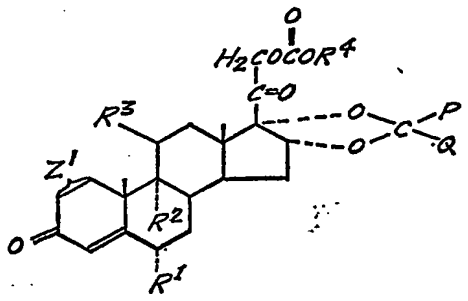
10. As a compound of Claim 8, 6α - fluoro - 11β,21 - dihydroxy - 16α,17α-isopropylidenedioxypregna - 1,4 - diene - 3,20 - dione 21-ethylcarbonate.

11. A compound of Claim 7 wherein R^2 is fluoro.

12. As a compound of Claim 11, 6α,9α - difluoro - 11β,21 - dihydroxy - 16α, 17α - isopropylidenedioxypregn - 4 - ene - 3,20 - dione 21-ethylcarbonate .

13. As a compound of Claim 11, 9α,11β - dichloro - 6α - fluoro - 21 - hydroxy-16α,17α - isopropylidenedioxypregna - 1,4 - diene - 3,20 - dione 21-ethylcarbonate.

14. The process for the preparation of a 21-carbonate ester of the general formula:



wherein

R^1 is fluoro or chloro;

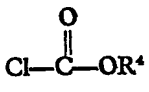
R^2 is hydrogen, fluoro or chloro;

R^3 is hydroxy or when R^2 is chloro, R^3 can be chloro;

R^4 is lower alkyl, cycloalkyl or aralkyl;

P and Q are hydrogen, lower alkyl, halogenated lower alkyl, monocyclic cycloalkyl, monocyclic aryl, monocyclic aryl lower alkyl, monocyclic heterocyclic or monocyclic heterocyclic lower alkyl or together with the carbon atom to which they are joined P and Q are cycloalkyl or monocyclic heterocyclic, and Z^1 is a single or double bond;

which comprises reacting together a corresponding 21-hydroxy starting steroid, and a chloroformate of the formula:



wherein R^4 is lower alkyl, cycloalkyl, or aralkyl.

15. A compound according to Claim 1 substantially as herein described and exemplified.

16. Process according to Claim 1 substantially as herein described and exemplified.

17. A 21-carbonate ester having the general formula as defined in Claim 14 when obtained by the process claimed in Claim 14 or Claim 16.

18. A therapeutic composition comprising a compound as claimed in any one of Claims 1 to 13 or Claim 15, or Claim 17 and a pharmaceutical excipient.

19. Therapeutic composition according to Claim 18 substantially as herein described.

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London W.C.2.
Agents for the Applicants.

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